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| <p>(54) Title: A DRUG COMPOSITION CONTAINING SODIUM PRAVASTATIN (57) Abstract The present invention relates to a drug composition containing sodium pravastatin and more particularly, to the drug composition containing further β-cyclodextrin as stabilizer for sodium pravastatin, thus enhancing the stability of sodium pravastatin which is unstable at high humidity and temperature.</p> | | |

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A DRUG COMPOSITION CONTAINING SODIUM PRAVASTATIN

5 BACKGROUND OF THE INVENTION

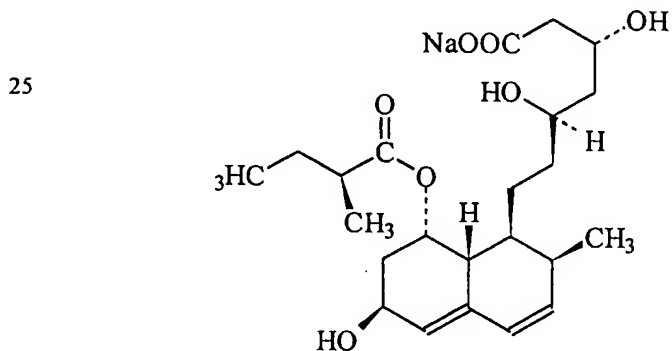
Field of the Invention

The present invention relates to a drug composition containing sodium pravastatin and more particularly, to the drug composition containing further β -cyclodextrin as stabilizer for sodium pravastatin, thus enhancing the stability of sodium pravastatin which is unstable at high humidity and temperature.

Description of the Related Art

Hyperlipidemia is a symptom characterized by high levels of lipids (cholesterol, neutral lipid, phospholipid, free fatty acid, etc.) in the plasma, and is associated with a number of serious disorders, notably arteriosclerosis, hypertension, ischemic heart disease, pancreatitis, etc.

To reduce the blood lipid levels, various drugs have been developed so far. As expressed in the following formula, sodium pravastatin among these drugs is known to be useful in the treatment of hyperlipidemia, since it serves to inhibit the activity of hydroxylmethyl glutaryl CoA reductase, which results in suppressing the synthesis of cholesterol. Sodium pravastatin generates its lactones and several isomers at high humidity and temperature.



For formulating a drug composition containing sodium pravastatin as

active ingredient, the conventional method has adopted its manufacturing process using some commonly available excipients such as lactose, silicon dioxide, sodium cross-carmellose, micro-crystallized cellulose and polyvinyl pyrrolidone.

5 For example, the general drug composition contains sodium pravastatin, lactose, micro-crystallized cellulose, polyvinyl pyrrolidone, sodium cross-carmellose and magnesium stearate (VIDAL, p.568(1997), ELISOR; VIDAL, pp.1750-1751(1997), VASTEN 20mg; ROTE LISTE 58 038(1996), PRAVASTIN 5mg/10mg/20mg). However, the drug composition consisting of
10 the above excipient is rapidly degraded at high humidity and temperature.

SUMMARY OF THE INVENTION

To overcome the shortcoming that the conventional method has faced with, the inventors have completed this invention with a notion that β -
15 cyclodextrin may encloses molecules with a low-molecular weight which may block any substances at the surrounding environment.

Accordingly, it is an object of this invention to provide a drug composition comprising sodium pravastatin, excipient, binder, lubricants, disintegrator and β -cyclodextrin, whereby enhancing the stability of sodium
20 pravastatin which is unstable at high humidity and temperature.

Description of the Drawings

Fig. 1a is a graph which shows the stability of drug composition prepared according to example 1 and comparative example 1 at 40°C.

25 Fig. 1b is a graph which shows the stability of drug composition prepared according to example 1 and comparative example 1 at 50°C.

Fig. 1c is a graph which shows the stability of drug composition prepared according to example 1 and comparative example 1 at 60°C.

Fig. 1d is a graph which shows the stability of drug composition prepared according to example 1 and comparative example 1 at 70°C.

Fig. 2a is a graph which shows the stability of drug composition prepared according to example 2 and comparative example 2 at 40°C.

Fig. 2b is a graph which shows the stability of drug composition prepared according to example 1 and comparative example 1 at 50°C.

Fig. 2c is a graph which shows the stability of drug composition prepared according to example 1 and comparative example 1 at 60°C.

Fig. 2d is a graph which shows the stability of drug composition prepared according to example 1 and comparative example 1 at 70°C.

Fig. 3a is a graph which shows the stability of drug composition prepared according to example 3 and comparative example 3 at 40°C.

Fig. 3b is a graph which shows the stability of drug composition prepared according to example 3 and comparative example 3 at 50°C.

Fig. 3c is a graph which shows the stability of drug composition prepared according to example 3 and comparative example 3 at 60°C.

Fig. 3d is a graph which shows the stability of drug composition prepared according to example 3 and comparative example 3 at 70°C.

Fig. 4a is a graph which shows the stability of drug composition prepared according to example 4 and comparative example 4 at 40°C.

Fig. 4b is a graph which shows the stability of drug composition prepared according to example 4 and comparative example 4 at 50°C.

Fig. 4c is a graph which shows the stability of drug composition prepared according to example 4 and comparative example 4 at 60°C.

Fig. 4d is a graph which shows the stability of drug composition prepared according to example 4 and comparative example 4 at 70°C.

Fig. 5a is a graph which shows the stability of drug composition

prepared according to example 5 and comparative example 5 at 40 °C.

Fig. 5b is a graph which shows the stability of drug composition prepared according to example 5 and comparative example 5 at 50 °C.

Fig. 5c is a graph which shows the stability of drug composition prepared according to example 5 and comparative example 5 at 60 °C.

Fig. 5d is a graph which shows the stability of drug composition prepared according to example 5 and comparative example 5 at 70 °C.

Fig. 6a is a graph which shows the stability of drug composition prepared according to example 1 and comparative example 1 under accelerated condition (40 °C / 75% R.H.) at 40 °C.

Fig. 6b is a graph which shows the stability of drug composition prepared according to example 2 and comparative example 2 under accelerated condition (40 °C / 75% R.H.) at 40 °C.

Fig. 6c is a graph which shows the stability of drug composition prepared according to example 3 and comparative example 3 under accelerated condition (40 °C / 75% R.H.) at 40 °C.

Fig. 6d is a graph which shows the stability of drug composition prepared according to example 4 and comparative example 4 under accelerated condition (40 °C / 75% R.H.) at 40 °C.

Fig. 6e is a graph which shows the stability of drug composition prepared according to example 5 and comparative example 5 under accelerated condition (40 °C / 75% R.H.) at 40 °C.

Fig. 7a is a graph which shows the stability of drug composition prepared in example 1 and A tablet™ at 40 °C.

Fig. 7b is a graph which shows the stability of drug composition prepared in example 1 and A tablet™ at 50 °C.

Fig. 7c is a graph which shows the stability of drug composition prepared in example 1 and A tablet™ at 60 °C.

Fig. 7d is a graph which shows the stability of drug composition prepared in example 1 and A tablet™ at 70°C.

Detailed Description of the Invention

5 This invention is characterized by a drug composition comprising sodium pravastatin as active ingredient and β -cyclodextrin as stabilizer as well as excipient, binder, disintegrator and lubricant.

This invention is explained in detail as set forth:

10 This invention pertains to the drug composition containing sodium pravastatin as active ingredient which has better stability in the mechanism that β -cyclodextrin encloses some molecules with a low-molecular weight to block any substances at the surrounding environment, thus preventing the rapid degradation of the drug composition at high temperature and humidity.

The drug composition of this invention comprises the following ingredients: sodium pravastatin as active ingredient; β -cyclodextrin as stabilizer; excipient such as lactose, starch and micro-crystallized cellulose; binder such as hydroxypropyl cellulose, non-crystallized cellulose, hydroxypropyl methyl cellulose and dextrin; disintegrator such as low-substituted hydroxypropyl cellulose and sodium cross-carmellose; and lubricant
20 such as magnesium stearate, talc and stearic acid.

The amount of sodium pravastatin as active ingredient, is advantageously in the range of 2 to 50wt% in proportion to the total drug composition, preferably in the range of 2 to 30wt%, at such levels, the drug composition serves to inhibit the activity of hydroxymethyl glutaryl CoA
25 reductase which results in suppressing the synthesis of cholesterol. If the amount of sodium pravastatin is less than 2wt%, a drug compliance is reduced due to increased weight of tablet; however, in case of exceeding 50wt%, a dose adjustment of each patient becomes difficult.

Since the sodium pravastatin is apt to form its lactones and several kinds of isomers at high humidity and temperature, β -cyclodextrin is added to the drug composition of this invention as a stabilizer so as to prevent such structural transformations. Unlike the conventional method using the common excipients which leads to the rapid degradation of a drug composition, the addition of β -cyclodextrin as a stabilizer according to this invention contributes to production of a drug composition with better stability at high humidity and temperature.

According to this invention, the amount of β -cyclodextrin is advantageously in the range of 50 to 5,000 weight parts in proportion to 100 weight parts of sodium pravastatin, preferably in the range of 100 to 3,000 weight parts. If the amount of β -cyclodextrin is less than 50 weight parts, insufficiently stabilized sodium pravastatin, is degraded at high humidity and temperature; in case of exceeding 5,000 weight parts, the formulation becomes difficult.

In addition to sodium pravastatin as active ingredient and β -cyclodextrin as stabilizer, the drug composition of this invention contains some additives such as excipient, binder, disintegrator and lubricant.

The excipient of this invention is at least one selected from the group consisting of corn starch, potato starch, wheat starch, lactose, white sugar, glucose, fructose, D-mannitol, precipitated calcium carbonate, micro-crystallized cellulose, dextrin and methyl cellulose; it is preferred that the amount of excipient is in the range of 5-90wt% to the total drug composition.

The binder of this invention is at least one selected from the group consisting of gelatin, methyl cellulose, non-crystallized cellulose, hydroxy cellulose, hydroxymethyl cellulose, glycerin, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, dextrin and polyvinyl alcohol; it is preferred

that the amount of binder is in the range of 2.5-35wt% to the total drug composition.

The disintegrator of this invention is at least one selected from the group consisting of hydroxypropyl methyl cellulose, hydroxypropyl starch, polyvinyl pyrrolidone, ethyl cellulose and low-substituted hydroxypropyl cellulose; it is preferred that the amount of disintegrator is in the range of 0.5-10wt% to the total drug composition.

The lubricant of this invention is at least one selected from the group consisting of stearic acid, magnesium stearate, talc, fluidized paraffin and rigid anhydrous silic acid; it is preferred that the amount of lubricant is in the range of 0.25-5wt% to the total drug composition. Also, some edible dye may be added to the drug composition depending on the objective of this invention.

The drug composition comprising the aforementioned ingredients is prepared as follows:

First, sodium pravastatin and β -cyclodextrin are ground in an appropriate container for tens of minutes, followed by the addition of one or more excipients. Then, for the purpose of use, the mixture is under wet granulation in the presence of a solution containing one or more binders and solvent (water, isopropanol, dichloromethane, etc.) and dried. As an alternative procedure, one or more lubricants and/or binders are added to the mixture of sodium pravastatin and β -cyclodextrin and under drying granulation using a rolling compactor.

After the procedure is completed, the drug composition of this invention is prepared with the addition of one or more disintegrators, lubricants or binders, if deemed necessary.

As such, the drug composition of this invention prepared as mentioned above, comprising sodium pravastatin as an active ingredient and β -cyclodextrin as stabilizer is mixed with some pharmaceutically acceptable

carriers to formulate a variety of dosage forms (e.g., tablet, capsule, powder, granule and pill) in the pharmaceutical field.

The examples of the carriers according to this invention include some pharmaceutically applicable carrier such as binder, lubricant, disintegrator, excipient, stabilizer and conspergative agent.

Further, to prevent the degradation of the drug composition by gastric acid during oral administration, the concurrent use of an antacid and enteric coated tablet and granule are recommended. It is recommended that the drug composition of this invention be orally administered as a desirable route (ABPI
10 Compendium of Data Sheets, VIDAL, ROTE LISTE, Physicians' Desk Reference).

According to this invention, a dose of the active ingredient varies depending on its absorption rate, inactivation rate and excretion rate, and other variations such as age, sex and conditions of patients, severity of disease, etc.
15 The regimen of the drug composition is recommended as follows: a) the usual dose of the drug composition for adult is 10-40mg per day before bedtime with initial dose of 10-20mg once daily (ABPI Compendium of Data Sheets, pp.1780-1782(1995-1996), LIPOSTAT TABLETS). The usual dose for adult is 10-40mg and in the case of the elderly patients, the usual dose is given at the dose of less
20 than 20mg (Physicians' Desk Reference, pp.732-735(1995), PRAVACHOL). Further, another initial dose is 10mg once per day with a maximum dose of 40mg in the evening (VIDAL, p.568(1997), ELISOR; pp.1750-1751(1997) VASTEN), while the initial dose is 5-10mg once daily with a maximum dose of 40mg (ROTE LISTE, 58 038(1996), PRAVASIN 5mg/10mg/20mg).

25 Based on the cited references, therefore, it is preferred that the drug composition of this invention is administered at a dose of 5-40mg once daily in the evening or before bedtime.

As described above, some physical strength is given to the drug

composition comprising sodium pravastatin as active ingredient and β -cyclodextrin as stabilizer, so formulated, for enclosing the active ingredient. As a result, the drug composition containing β -cyclodextrin shows excellent stability at high temperature and humidity (Fig. 1a-7d).

5 When the drug composition of this invention is compared with comparative examples and A tablet without β -cyclodextrin as shown in Fig. 1a-5d and Fig. 7a-7d, it is evident that the drug composition of this invention has much better stability on the temperature than that of the conventional drug composition. Also, for stability on humidity, the same results were revealed in
10 Fig. 6a-6e. Furthermore, the process for preparing the drug composition of this invention may utilize the existing machine such as a rolling compactor in mass-production, thereby improving the aspects of economics such as the additional cost for production.

The following specific examples are intended to be illustrative of the
15 invention and should not be construed as limiting the scope of the invention as defined by appended claims.

Example 1

| | | |
|----|---|----------|
| | Sodium pravastatin | 5mg |
| 20 | β -cyclodextrin | 120.09mg |
| | Hydroxypropyl cellulose | 5mg |
| | Low-substituted hydroxypropyl cellulose | 13.5mg |
| | Lactose | 48.51mg |
| | Magnesium stearate | 0.9mg |

25 A mixture of sodium pravastatin and β -cyclodextrin was ground in a reactor for 20 mins. With the addition of lactose, the reacting solution was well mixed and agglomerated in an aqueous solution of a binder solution (hydroxypropyl cellulose solution). The solution was dried in an oven at 30-

40°C and sized with a sieve of No. 20. With the addition of low-substituted hydroxypropyl cellulose and magnesium stearate, the mixture was well mixed for its tableting process.

5 Example 2

| | | |
|----|---|----------|
| | Sodium pravastatin | 5mg |
| | β -cyclodextrin | 127.09mg |
| | Hydroxypropyl cellulose | 5mg |
| | Low-substituted hydroxypropyl cellulose | 13.5mg |
| 10 | Lactose | 30.0mg |
| | Corn starch | 18.51mg |
| | Magnesium stearate | 0.9mg |

A mixture of sodium pravastatin and β -cyclodextrin was ground in a reactor for 20 mins. With the addition of lactose and corn starch, the reacting
15 solution was well mixed and agglomerated in an aqueous solution of a binder solution (hydroxypropyl cellulose solution). The solution was dried in an oven at 30-40°C and sized with a sieve of No. 20. With the addition of low-substituted hydroxypropyl cellulose and magnesium stearate, the mixture was well mixed for its tableting process.

20

Example 3

| | | |
|----|---|----------|
| | Ssodium pravastatin | 5mg |
| | β -cyclodextrin | 127.09mg |
| | Rigid anhydrous silicic acid | 1.75mg |
| 25 | Low-substituted hydroxypropyl cellulose | 10.0mg |
| | Lactose | 30.0mg |
| | Magnesium stearate | 1.6mg |

A mixture of sodium pravastatin and β -cyclodextrin was ground in a

reactor for 20 mins. With the addition of lactose, rigid anhydrous silicic acid and magnesium stearate (0.8mg), the reacting solution was well mixed and subjected to rolling compactor, finally preparing dried granules. With the addition of low-substituted hydroxypropyl cellulose and magnesium stearate, the mixture was well mixed for its tableting process.

Example 4

| | | |
|----|---|----------|
| | Sodium pravastatin | 5mg |
| | β -cyclodextrin | 127.09mg |
| 10 | Low-substituted hydroxypropyl cellulose | 10.0mg |
| | Lactose | 20.07mg |
| | Corn starch | 28.0mg |
| | Dextrin | 7.8mg |
| | Red-dye # 3 | 0.12mg |
| 15 | Blue-dye #1 aluminium lake | 0.12mg |
| | Magnesium stearate | 1.6mg |

A mixture of sodium pravastatin and β -cyclodextrin was ground in a reactor for 20 mins. With the addition of lactose and corn starch (14.0mg), the reacting solution was well mixed and agglomerated in an aqueous solution of a binder solution (dextrin) containing dyes (red-dye # 3 and blue-dye #1 aluminium lake), followed by drying in oven at 30-40°C. With the addition of remaining corn starch (14.0mg), low-substituted hydroxypropyl cellulose and magnesium stearate, the mixture was well mixed for its tableting process.

Example 5

| | | |
|--|-----------------------|----------|
| | Sodium pravastatin | 5mg |
| | β -cyclodextrin | 127.09mg |
| | Lactose | 30.31mg |

| | |
|--------------------|--------|
| Potato starch | 30.0mg |
| Polyvinyl alcohol | 7.8mg |
| Magnesium stearate | 1.6mg |

5 A mixture of sodium pravastatin and β -cyclodextrin was ground in a reactor for 20 mins. With the addition of lactose and potato starch, the reacting solution was well mixed and agglomerated in an aqueous solution of a binder solution (polyvinyl alcohol), followed by drying in oven at 30-40°C. With the addition of magnesium stearate, the mixture was well mixed for its tableting
10 process.

Comparative example 1

| | |
|--|----------|
| Sodium pravastatin | 5mg |
| Hydroxypropyl cellulose | 127.09mg |
| 15 Low-substituted hydroxypropyl cellulose | 10.0mg |
| Lactose | 175.6mg |
| Magnesium stearate | 0.9mg |

A mixture of sodium pravastatin and lactose was well mixed and agglomerated in an aqueous solution of a binder solution (hydroxypropyl
20 cellulose), followed by drying in oven at 30-40°C. Then, the dried preparation was sized with a sieve of No. 20. With the addition of low-substituted hydroxypropyl cellulose and magnesium stearate, the mixture was well mixed for its tableting process.

25 Comparative example 2

| | |
|---|--------|
| Sodium pravastatin | 5mg |
| Hydroxypropyl cellulose | 5mg |
| Low-substituted hydroxypropyl cellulose | 13.5mg |

| | |
|--------------------|----------|
| Lactose | 157.09mg |
| Corn starch | 18.51mg |
| Magnesium stearate | 0.9mg |

A mixture of sodium pravastatin, lactose and corn starch was well
5 mixed and agglomerated in an aqueous solution of a binder solution
(hydroxypropyl cellulose), followed by drying in oven at 30-40°C. Then, the
dried preparation was sized with a sieve of No. 20. With the addition of low-
substituted hydroxypropyl cellulose and magnesium stearate, the mixture was
well mixed for its tableting process.

10

Comparative example 3

| | |
|---|----------|
| Sodium pravastatin | 5mg |
| Rigid anhydrous silicic acid | 1.75mg |
| Low-substituted hydroxypropyl cellulose | 10.0mg |
| 15 Lactose | 181.65mg |
| Magnesium stearate | 1.6mg |

With the addition of sodium pravastatin, rigid anhydrous silicic acid
and magnesium stearate (0.8mg), the reacting solution was well mixed and
subjected to rolling compactor, finally preparing dried granules. With the
20 addition of low-substituted hydroxypropyl cellulose and magnesium stearate
(0.8mg), the mixture was well mixed for its tableting process.

Comparative example 4

| | |
|--|----------|
| Sodium pravastatin | 5mg |
| 25 Low-substituted hydroxypropyl cellulose | 10.0mg |
| Lactose | 120.27mg |
| Corn starch | 55.09mg |
| Dextrin | 7.8mg |

| | |
|----------------------------|--------|
| Red-dye # 3 | 0.12mg |
| Blue-dye #1 aluminium lake | 0.12mg |
| Magnesium stearate | 1.6mg |

5 With the addition of sodium pravastatin, lactose and corn starch (half of the content), the reacting solution was well mixed and agglomerated in an aqueous solution of a binder solution (dextrin) containing dyes (red-dye # 3 and blue-dye #1 aluminium lake), followed by drying in oven at 30-40°C. With the addition of remaining corn starch, low-substituted hydroxypropyl cellulose
10 and magnesium stearate, the mixture was well mixed for its tableting process.

Comparative example 5

| | |
|--------------------|----------|
| Sodium pravastatin | 5mg |
| Lactose | 130.31mg |
| 15 Potato starch | 57.09mg |
| Polyvinyl alcohol | 5.7mg |
| Magnesium stearate | 1.9mg |

With the addition of sodium pravastatin, lactose and potato starch, the reacting solution was well mixed and agglomerated in an aqueous solution of a
20 binder solution (polyvinyl alcohol), followed by drying in oven at 30-40°C. With the addition of magnesium stearate, the mixture was well mixed for its tableting process.

Test 1

25 In order to confirm the effect of this invention, final preparations were tested under rigorous temperature condition (40, 50, 60 and 70°C) with regard to an alteration of content and degraded products by using the following machine, and the results are shown in Table 1a-1e and Fig. 1a-5d:

1) High performance liquid chromatography : Waters 510

Detector: ultraviolet absorption spectrophotometer (238nm)

Column: Cosmosil C₁₈

Mobile phase: methanol · H₂O · TEA · acetic acid (500:500:1:1)

Flow rate: 1.5ml/min

Injection amount: 5 μ l

2) Autosampler: Waters 717

3) Integrator: Waters 740

4) Detector: Waters 486

5) Oven

SY-IN.G (SUN YOUNG Co., Korea), if treated at 40 °C

VO-C-2 (Space Science Co., Korea), if treated at 50 °C and 60 °C

NDO-600-ND (EYELA Co., Korea), if treated at 70 °C

6) Life tester : JEIO TECH. Co. Ltd., TH-10

Table 1a

| Category | | At start | After 7 days | After 15 days | After 23 days | After 29 days |
|---------------------------------------|-------|----------|-----------------|------------------|------------------|------------------|
| Exam. 1 (remained, %)* | 40 °C | 100 | 99.8 | 99.3 | 98.9 | 98.0 |
| | 50 °C | 100 | 97.9 | 97.8 | 96.4 | 95.6 |
| | 60 °C | 100 | 99.5 | 97.8 | 91.3 | 90.0 |
| | 70 °C | 100 | 97.4 | 89.8 | 84.1 | 80.1 |
| Comp. Exam. 1 (remained, %)* | 40 °C | 100 | 99.1 | 97.9 | 95.4 | 93.1 |
| | 50 °C | 100 | 93.7 | 92.0 | 91.9 | 89.0 |
| | 60 °C | 100 | 93.3 | 92.3 | 86.5 | 83.2 |
| | 70 °C | 100 | 91.5 | 78.8 | 67.5 | 64.8 |

* the remaining amount of sodium pravastatin among the pharmaceutical composition

Table 1b

| Category | | At start | After 7 days | After 15 days | After 23 days | After 29 days |
|----------------------------------|------|----------|--------------|---------------|---------------|---------------|
| Exam. 2 (remainder, %)* | 40°C | 100 | 99.7 | 99.0 | 98.7 | 98.6 |
| | 50°C | 100 | 98.9 | 97.5 | 96.0 | 95.3 |
| | 60°C | 100 | 98.8 | 97.3 | 92.0 | 89.9 |
| | 70°C | 100 | 97.0 | 88.5 | 83.9 | 79.2 |
| Comp. Exam. 2 (remainder, %)* | 40°C | 100 | 99.0 | 97.5 | 95.2 | 94.0 |
| | 50°C | 100 | 92.8 | 91.5 | 91.0 | 89.2 |
| | 60°C | 100 | 91.2 | 90.6 | 88.5 | 82.5 |
| | 70°C | 100 | 90.9 | 80.3 | 72.0 | 63.9 |

* the remaining amount of sodium pravastatin among the pharmaceutical composition

Table 1c

| Category | | At start | After 7 days | After 15 days | After 23 days | After 29 days |
|------------------------------------|-------|----------|--------------|---------------|---------------|---------------|
| Exam. 3 (remained, %)* | 40 °C | 100 | 99.9 | 99.5 | 99.0 | 98.6 |
| | 50 °C | 100 | 98.2 | 97.8 | 97.0 | 96.0 |
| | 60 °C | 100 | 98.2 | 97.0 | 93.5 | 90.2 |
| | 70 °C | 100 | 96.2 | 89.6 | 82.0 | 75.3 |
| Comp. Exam. 3 (remained, %)* | 40 °C | 100 | 99.2 | 98.1 | 96.7 | 95.5 |
| | 50 °C | 100 | 93.5 | 92.9 | 92.1 | 90.8 |
| | 60 °C | 100 | 91.3 | 90.2 | 89.3 | 80.5 |
| | 70 °C | 100 | 89.6 | 79.6 | 70.3 | 65.0 |

* the remaining amount of sodium pravastatin among the pharmaceutical composition

Table 1d

| Category | | At start | After 7 days | After 15 days | After 23 days | After 29 days |
|-------------------------------------|------|----------|--------------|---------------|---------------|---------------|
| Exam. 4 (remainder, %)* | 40°C | 100 | 99.2 | 98.8 | 96.5 | 96.0 |
| | 50°C | 100 | 98.6 | 97.7 | 95.8 | 95.2 |
| | 60°C | 100 | 98.0 | 96.8 | 92.6 | 88.8 |
| | 70°C | 100 | 96.0 | 88.2 | 80.2 | 79.6 |
| Comp. Exam. 4 (remainder, %)* | 40°C | 100 | 99.0 | 98.0 | 95.0 | 94.5 |
| | 50°C | 100 | 92.3 | 91.5 | 90.2 | 89.6 |
| | 60°C | 100 | 90.6 | 89.9 | 86.0 | 80.0 |
| | 70°C | 100 | 88.5 | 80.3 | 68.8 | 60.2 |

* the remaining amount of sodium pravastatin among the pharmaceutical composition

Table 1e

| Category | | At start | After 7 days | After 15 days | After 23 days | After 29 days |
|---------------------------------|------|----------|--------------|---------------|---------------|---------------|
| Exam. 5 (remained, %)* | 40°C | 100 | 99.7 | 99.0 | 99.0 | 98.5 |
| | 50°C | 100 | 98.9 | 97.0 | 97.2 | 95.2 |
| | 60°C | 100 | 98.5 | 97.5 | 93.3 | 89.9 |
| | 70°C | 100 | 96.5 | 88.8 | 83.2 | 80.2 |
| Comp. Exam. 5 (remained, %)* | 40°C | 100 | 99.0 | 98.0 | 96.8 | 94.5 |
| | 50°C | 100 | 94.0 | 93.2 | 92.8 | 90.0 |
| | 60°C | 100 | 93.0 | 92.6 | 89.2 | 80.0 |
| | 70°C | 100 | 90.5 | 80.9 | 75.5 | 70.0 |

* the remaining amount of sodium pravastatin among the pharmaceutical composition

5 Test 2

In order to confirm the effect of this invention, final preparations were tested under accelerated condition (40°C / 75% R.H.) with regard to an alteration of content and decomposed products, and the results are shown in Table 2 and Fig. 6a-6e:

Table 2

| Category | | At start | After 1 month | After 2 months | After 3 months |
|----------------|--------------|----------|---------------|----------------|----------------|
| Remainder* (%) | Exam. 1 | 100 | 97.5 | 93.1 | 90.0 |
| | Exam. 2 | 100 | 97.8 | 92.9 | 90.3 |
| | Exam. 3 | 100 | 98.0 | 92.5 | 89.1 |
| | Exam. 4 | 100 | 95.0 | 90.1 | 87.1 |
| | Exam. 5 | 100 | 96.6 | 93.5 | 89.0 |
| | Com. Exam. 1 | 100 | 92.0 | 89.5 | 84.4 |
| | Com. Exam. 2 | 100 | 92.5 | 88.5 | 83.1 |
| | Com. Exam. 3 | 100 | 93.1 | 88.0 | 82.3 |
| | Com. Exam. 4 | 100 | 94.0 | 86.9 | 80.0 |
| | Com. Exam. 5 | 100 | 91.3 | 89.3 | 83.0 |

* the remaining amount of sodium pravastatin among the pharmaceutical composition

5 Test 3

In order to confirm the effect of this invention, final preparation (prepared in example 1) and A tablet™ (commercial product, Korea) were tested under rigorous temperature condition (40, 50, 60 and 70℃) with regard to an alteration of content and decomposed products, and the results are shown in Table 3 and Fig. 7a-7d:

Table 3

| Category | | At start | After 7 days | After 15 days | After 23 days | After 29 days |
|---------------------------------|------|----------|--------------|---------------|---------------|---------------|
| Exam. 1 (remainder, %)* | 40°C | 100 | 99.8 | 99.3 | 98.9 | 98.0 |
| | 50°C | 100 | 97.9 | 97.8 | 96.4 | 95.6 |
| | 60°C | 100 | 99.5 | 97.8 | 91.3 | 90.0 |
| | 70°C | 100 | 97.4 | 89.8 | 84.1 | 80.1 |
| A Tablet™ (remainder, %)* | 40°C | 100 | 99.4 | 99.0 | 98.6 | 97.5 |
| | 50°C | 100 | 98.0 | 96.9 | 93.6 | 90.1 |
| | 60°C | 100 | 98.5 | 95.1 | 89.2 | 87.5 |
| | 70°C | 100 | 89.1 | 84.3 | 76.8 | 65.9 |

* the remaining amount of sodium pravastatin among the pharmaceutical composition

As discussed above, the pharmaceutical composition of this invention, comprising sodium pravastatin as active ingredient and β -cyclodextrin as stabilizer, has excellent stability at high humidity and temperature so that it prohibits the sodium pravastatin from decomposing rapidly, and may employ the existing machine in mass production, thereby improving the aspects of economics such as the additional cost for production.

CLAIMS

What is claimed is:

1. A drug composition comprising sodium pravastatin as active ingredient,
5 excipient, binder, disintegrator and lubricants, characterized in that the
composition contains β -cyclodextrin as stabilizer for the sodium pravastatin.
2. The drug composition according to claim 1, wherein the amount of sodium
pravastatin is in the range of 2-50wt% to the total drug composition.
- 10 3. The drug composition according to claim 1, wherein the amount of β -
cyclodextrin is 50-5,000 weight part to 100 weight part of the sodium
pravastatin.
- 15 4. The drug composition according to claim 1, wherein the amount of excipient
is in the range of 5-90wt% to the total drug composition.
5. The drug composition according to claim 1 or 4, wherein the excipient is at
least one selected from the group consisting of corn starch, potato starch, wheat
20 starch, lactose, white sugar, glucose, fructose, D-mannitol, precipitated calcium
carbonate, micro-crystallized cellulose, dextrin and methyl cellulose.
6. The drug composition according to claim 1, wherein the amount of binder is
in the range of 2.5-35wt% to the total drug composition.
- 25 7. The drug composition according to claim 1 or 6, wherein the binder is at least
one selected from the group consisting of gelatin, methyl cellulose, non-
crystallized cellulose, hydroxy cellulose, hydroxymethyl cellulose, glycerin,

hydroxypropyl cellulose, hydroxypropyl methyl cellulose, dextrin and polyvinyl alcohol.

5 8. The drug composition according to claim 1, wherein the amount of disintegrator is in the range of 0.5-10wt% to the total drug composition.

9. The drug composition according to claim 1 or 8, wherein the disintegrator is at least one selected from the group consisting of hydroxypropyl methyl
10 cellulose, hydroxypropyl starch, polyvinyl pyrrolidone, ethyl cellulose and low-substituted hydroxypropyl cellulose.

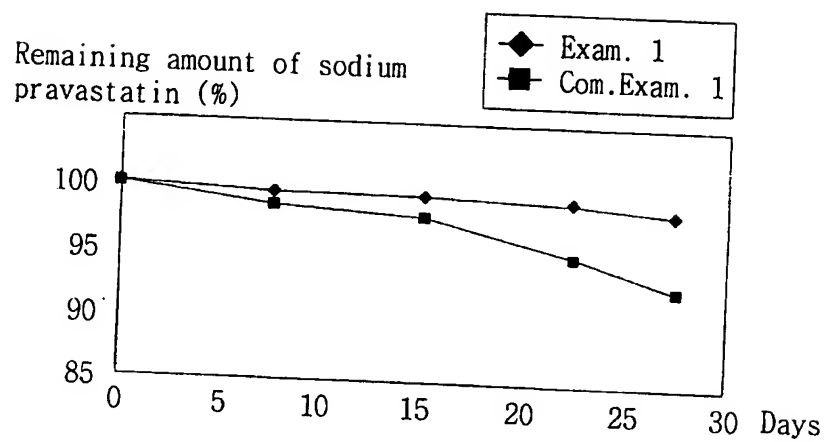
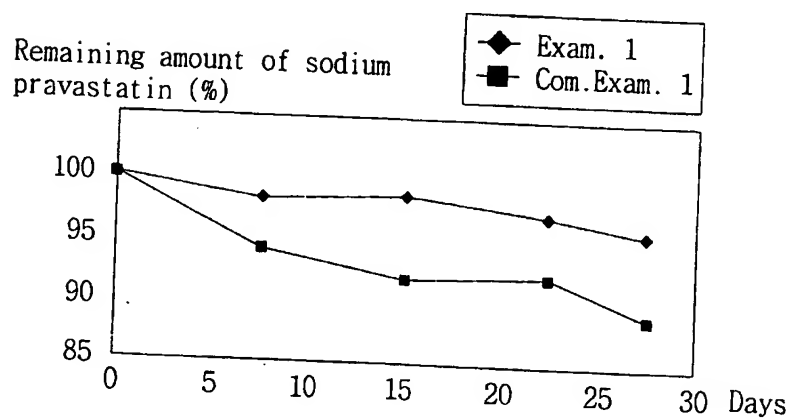
10. The drug composition according to claim 1, wherein the amount of lubricants is in the range of 0.25-5wt% to the total drug composition.

15

11. The drug composition according to claim 1 or 10, wherein the lubricants is at least one selected from the group consisting of stearic acid, magnesium stearate, talc, fluidized paraffin and rigid anhydrous silic acid.

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FIGURE**Fig. 1a****Fig. 1b**

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Fig. 1c

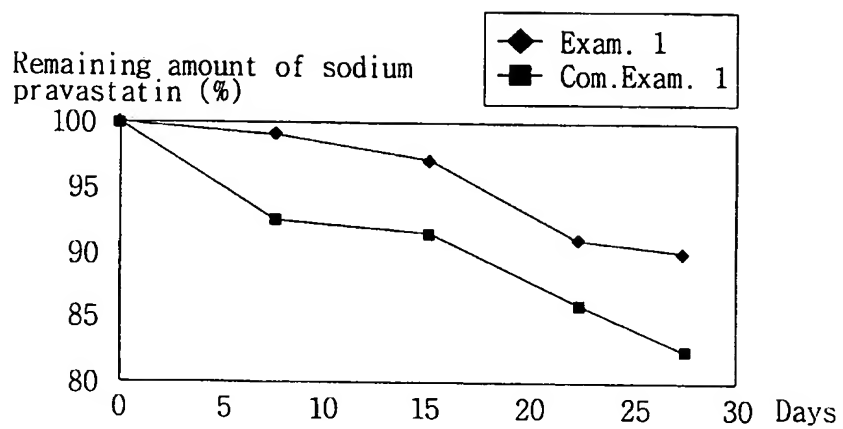
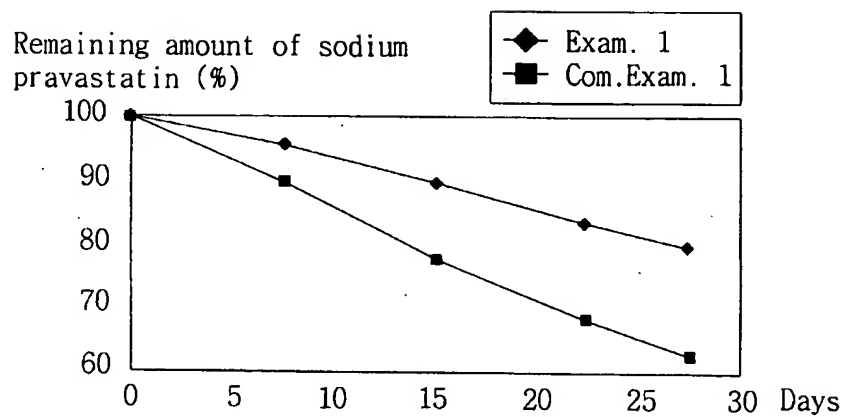


Fig. 1d



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Fig. 2a

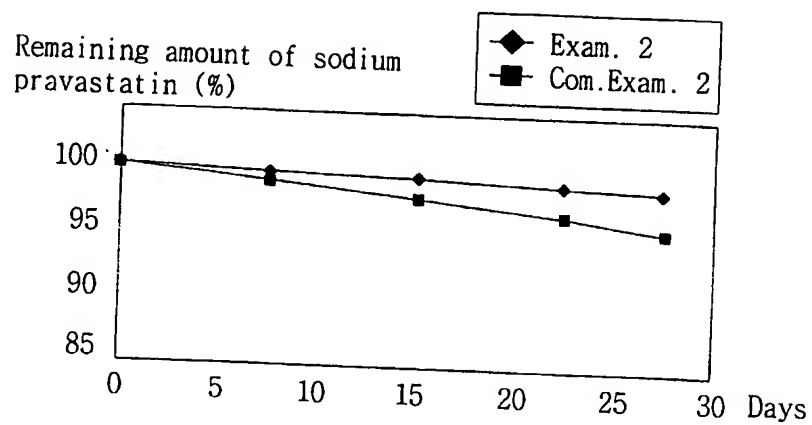
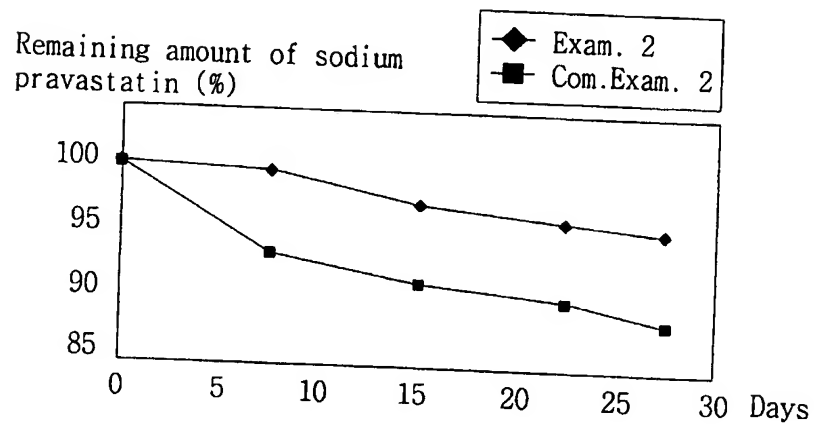


Fig. 2b



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Fig. 2c

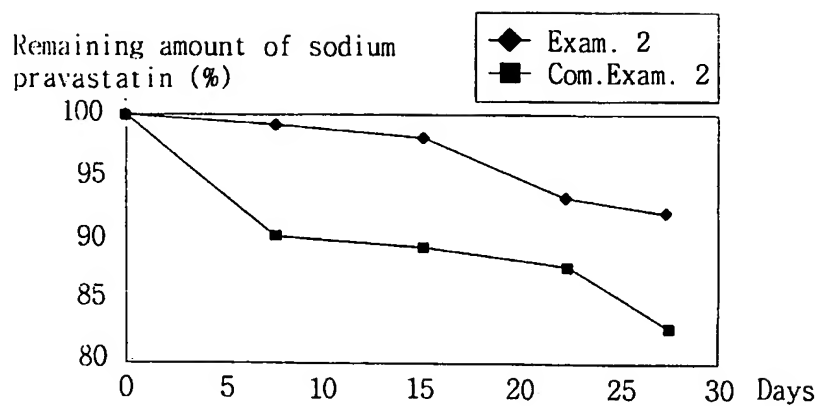
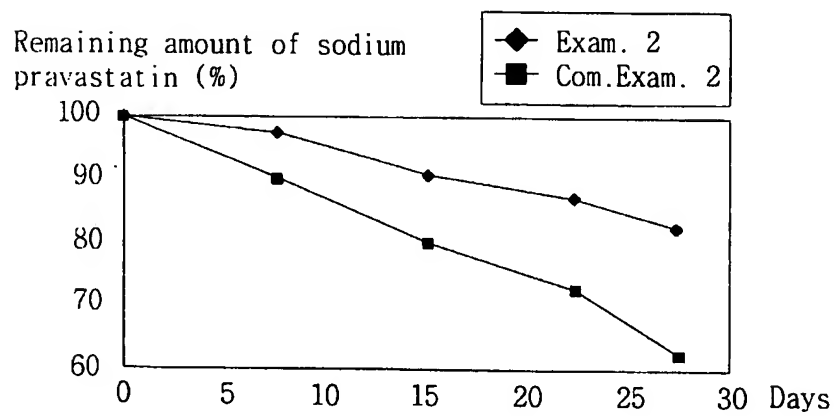
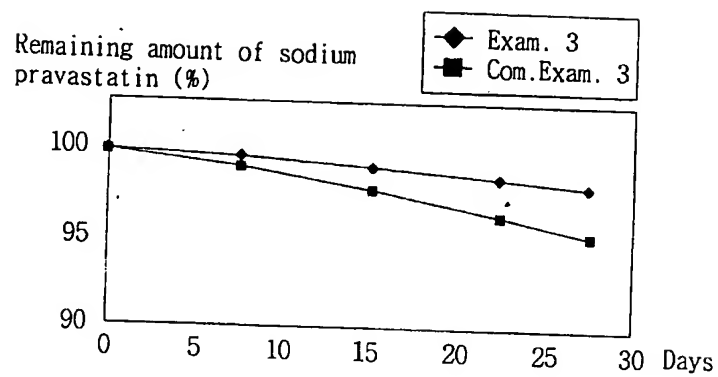
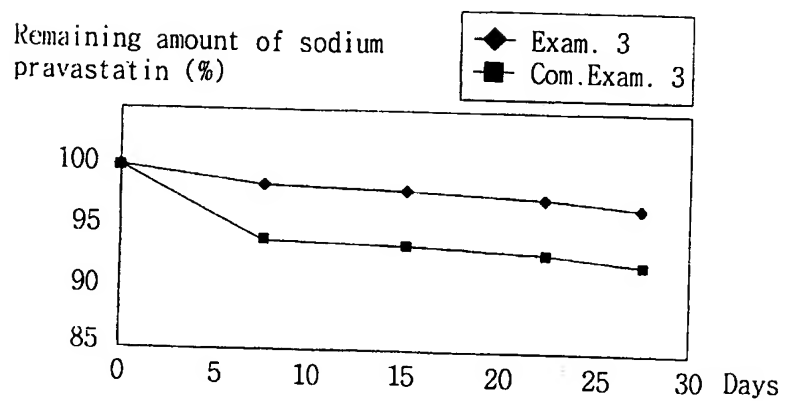


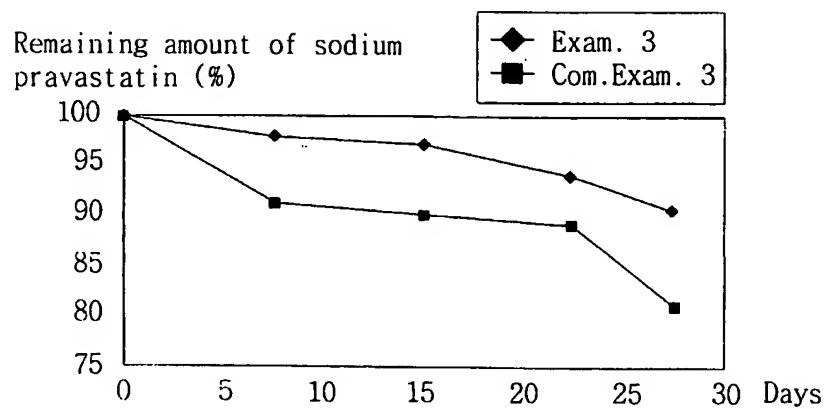
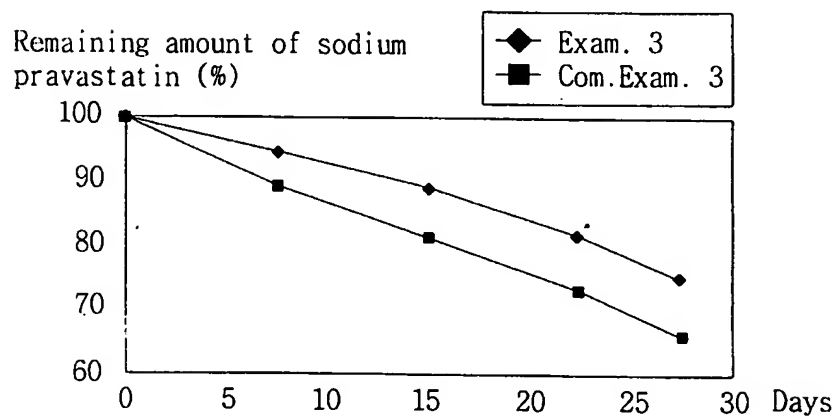
Fig. 2d



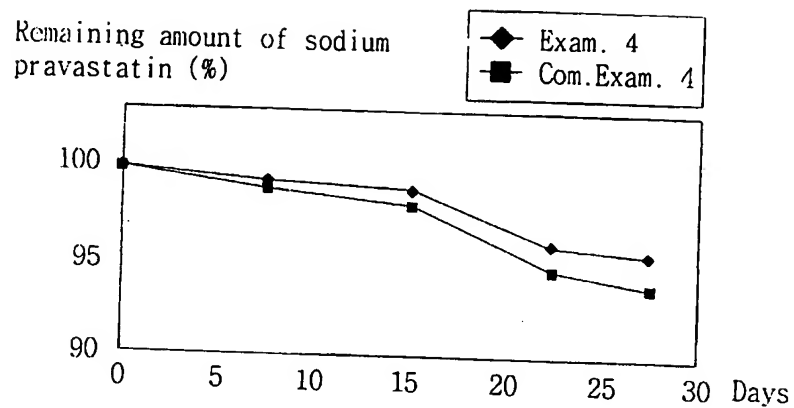
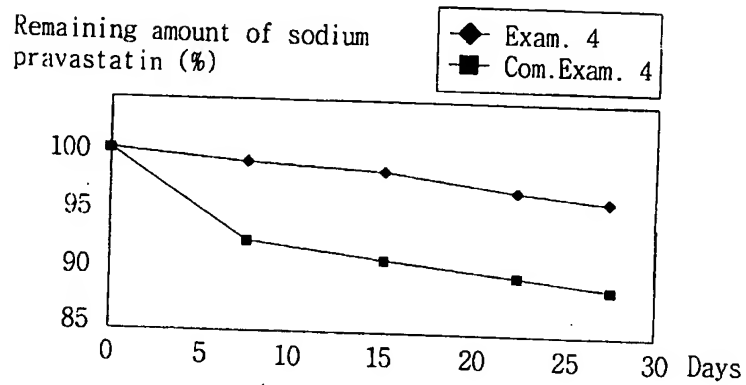
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Fig. 3a**Fig. 3b**

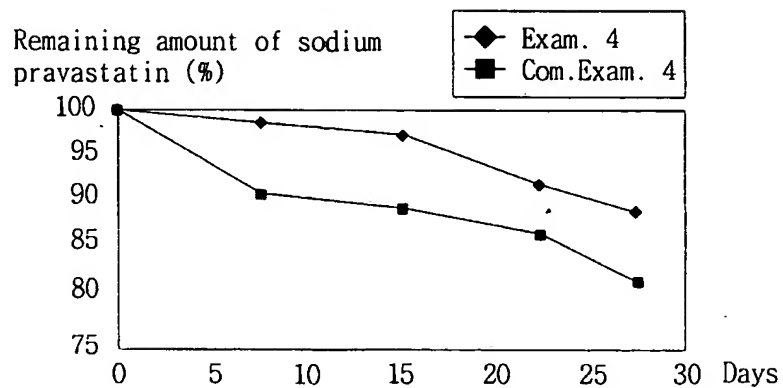
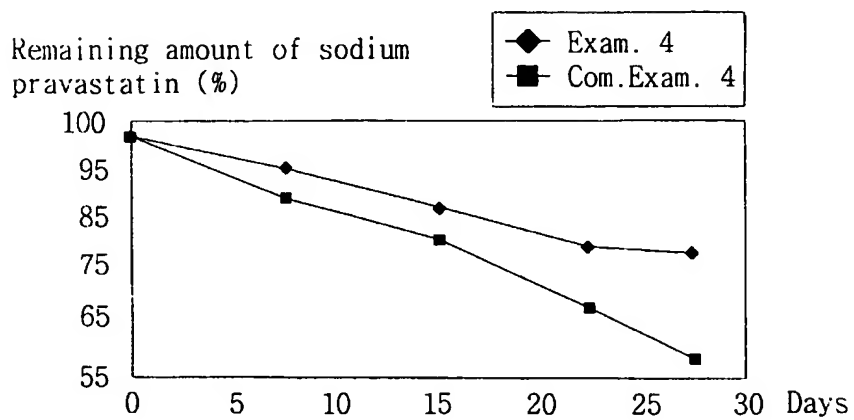
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Fig. 3c**Fig. 3d**

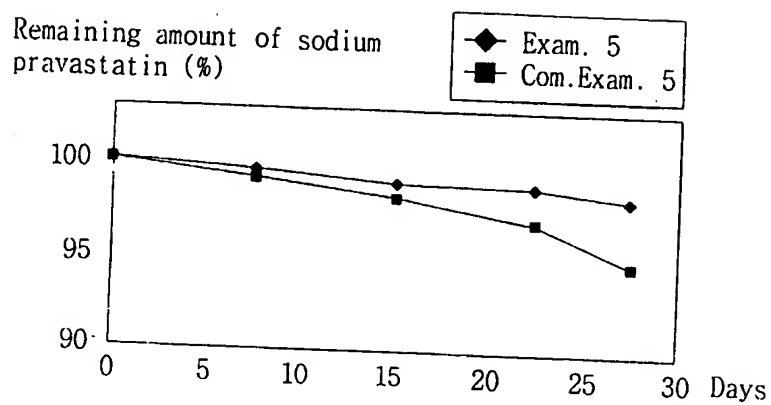
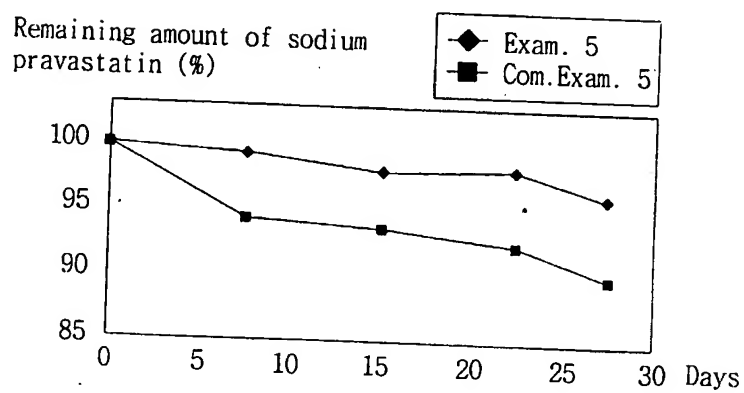
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Fig. 4a**Fig. 4b**

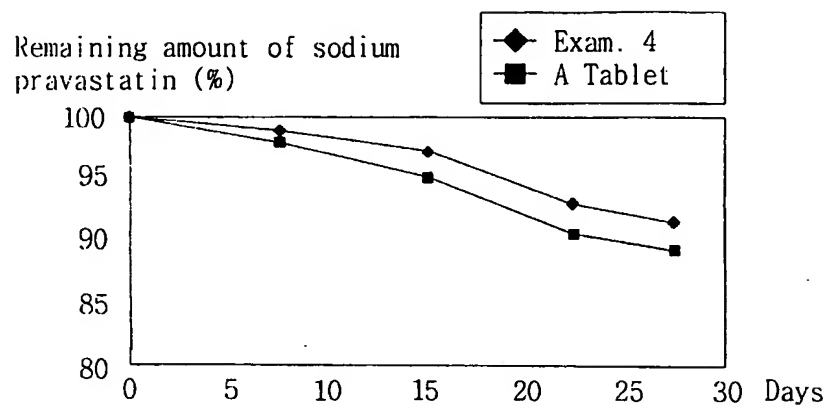
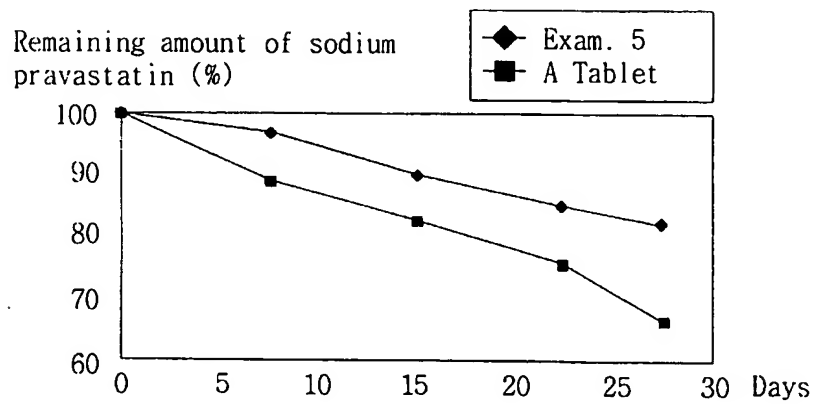
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Fig. 4c**Fig. 4d**

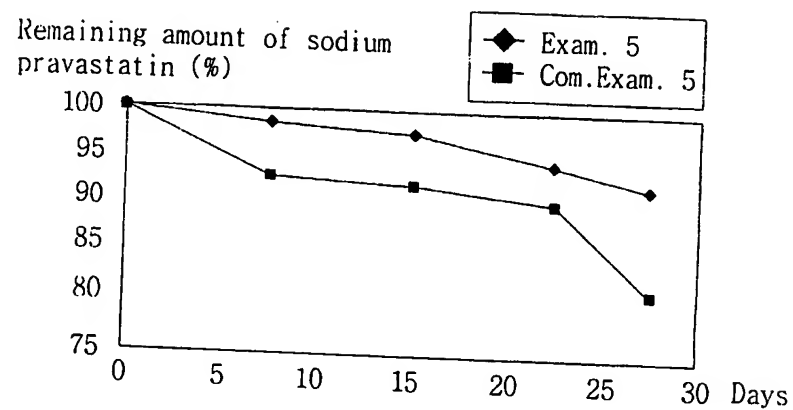
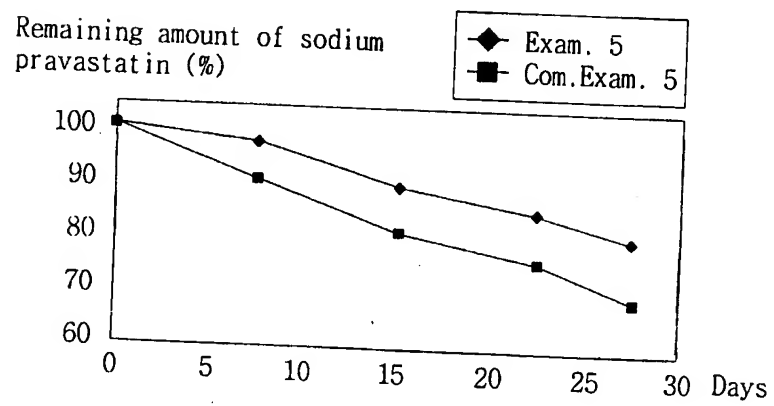
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Fig. 5a**Fig. 5b**

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Fig. 5c**Fig. 5d**

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Fig. 6a**Fig. 6b**

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Fig. 6c

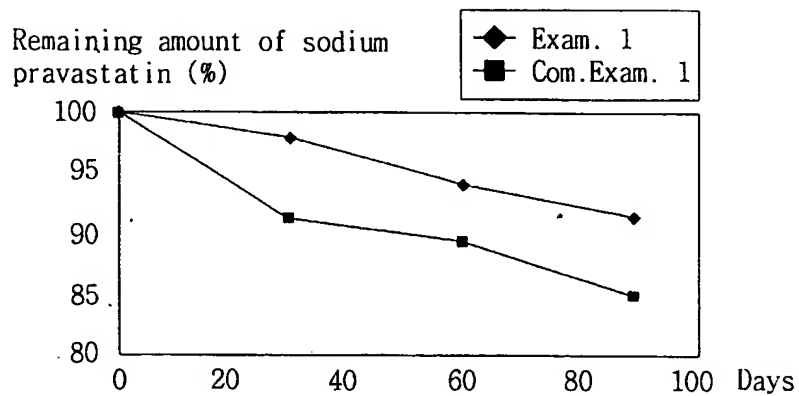
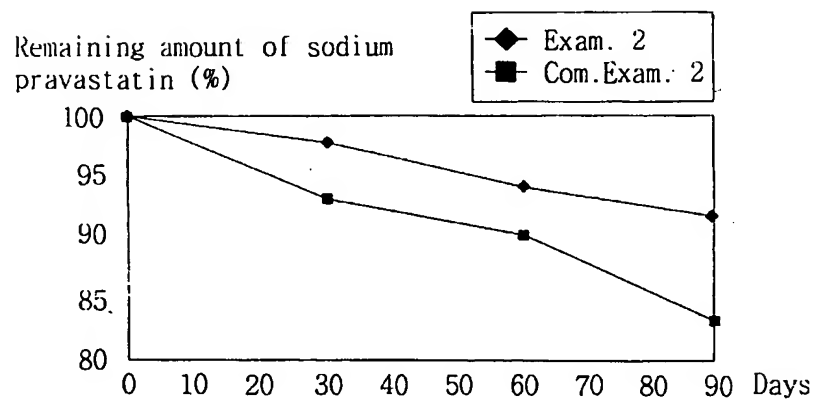
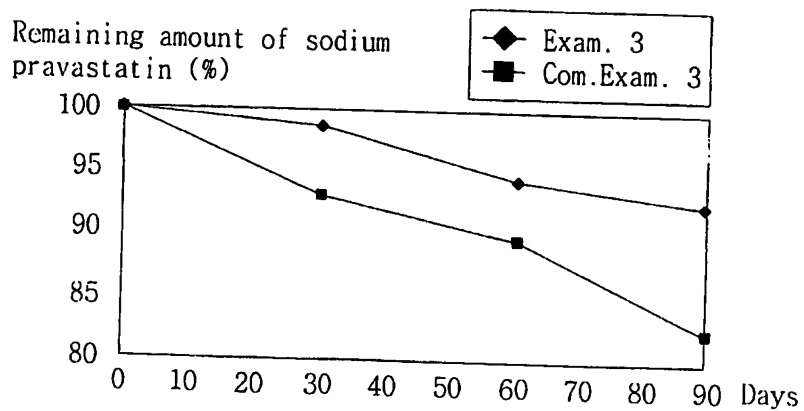
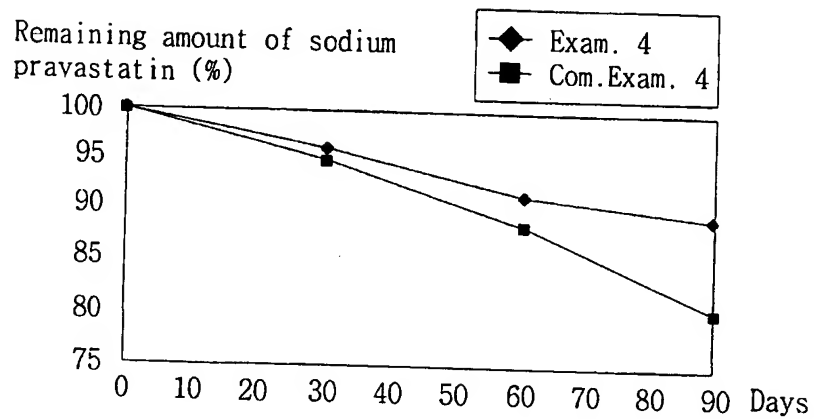


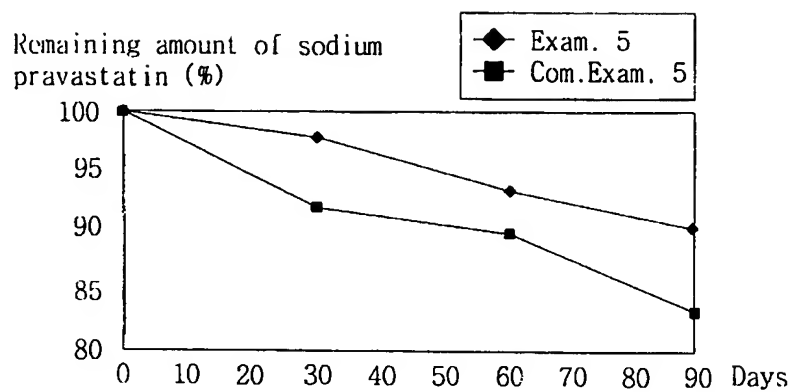
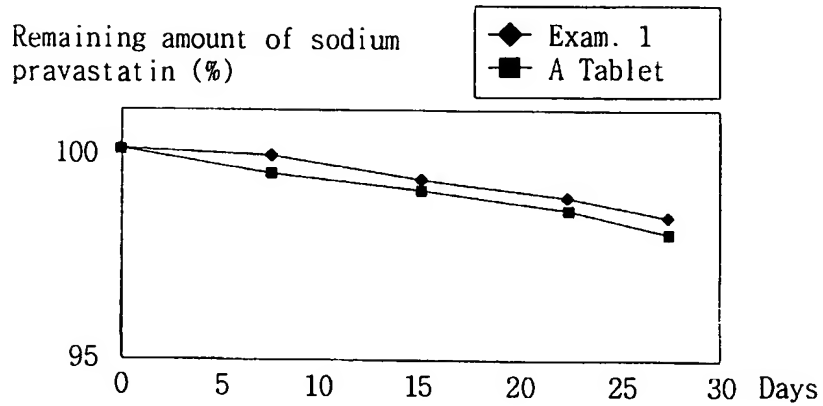
Fig. 6d



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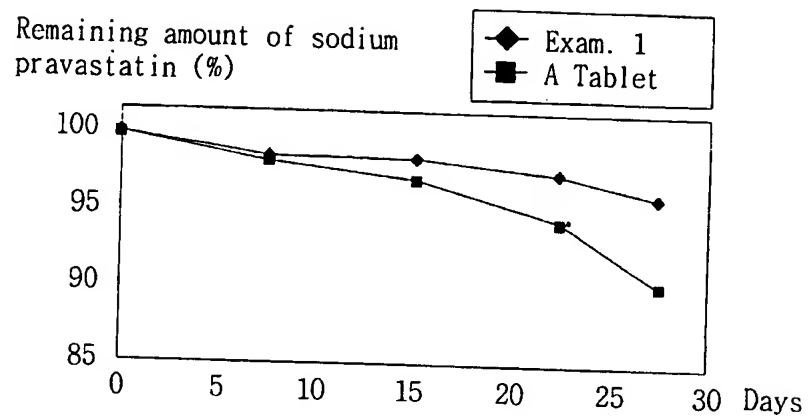
Fig. 6e**Fig. 7a**

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Fig. 7b**Fig. 7c**

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Fig. 7d



INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR 99/00157

A. CLASSIFICATION OF SUBJECT MATTER

IPC⁶: A 61 K 47/40, 31/19, 9/20

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC⁶: A 61 K 47/40, 31/19, 9/20

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WPI, CAS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|-----------|---|-----------------------|
| A | EP 0 336 298 A1 (E. R. SQIBB & SONS, INC.) 11 October 1989 (11.10.89), totality. | 1, 2, 4 - 11 |
| A | DD 232 198 A1 (VEB JENAPHARM) 22 January 1986 (22.01.86), claim; examples 1 - 3. | 1, 5, 11 |
| A | DE 32 23 232 A1 (KUREHA KAGAKU KOGYO K.K.) 03 February 1983 (03.02.83), claims 1 - 5. | 1, 2 |
| | ---- | |

☐ Further documents are listed in the continuation of Box C.☒ See patent family annex.

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Date of the actual completion of the international search

28 June 1999 (28.06.99)

Date of mailing of the international search report

27.July 1999 (27.07.99)

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INTERNATIONAL SEARCH REPORT

Information on patent family members

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| In Recherchenbericht angeführtes Patentdokument Patent document cited in search report Document de brevet cité dans le rapport de recherche | Datum der Veröffentlichung Publication date Date de publication | Mitglied(er) der Patentfamilie Patent family member(s) Membre(s) de la famille de brevets | Datum der Veröffentlichung Publication date Date de publication |
|--|--|--|--|
| EP A1 336298 | 11-10-1989 | AT E 79030 AU A1 30276/89 AU B2 624117 CA A1 1323836 CN A 1036508 CN B 1026861 DE C0 68902344 DE T2 68902344 DK A0 1556/89 DK A 1556/89 EP B1 336298 HK A 400793 IE B 62956 JP A2 2006406 NZ A 228076 SG A 1072/92 US A 5030447 ZA A 8901424 US A 5180589 CY A 1675 | 15-08-1992 05-10-1989 04-06-1992 02-11-1993 25-10-1989 07-12-1994 10-09-1992 07-01-1993 30-03-1989 01-10-1989 05-08-1992 30-04-1993 08-03-1995 10-01-1990 26-04-1991 24-12-1992 09-07-1991 25-10-1989 19-01-1993 10-10-1993 |
| DD A1 232198 | 22-01-1986 | keine - none - rien | |
| DE A1 3226232 | 03-02-1983 | GB A1 2104907 JP A2 58013541 US A 4438106 | 16-03-1983 26-01-1983 20-03-1984 |